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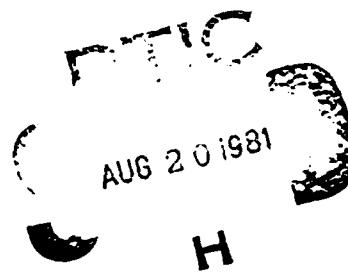
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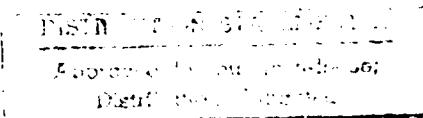
PHYSIOLOGIC ASPECTS OF PORCINE HEMORRHAGE

II. Alterations in Heart Rate and Arterial Pressure during Fifty Percent  
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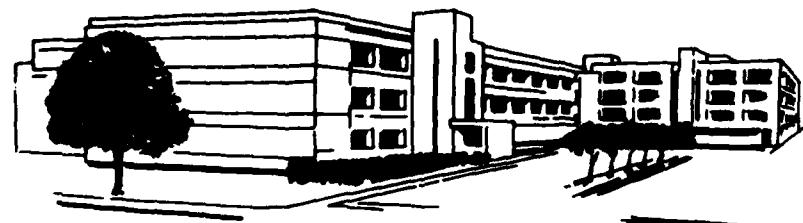
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**Physiologic Aspects of Porcine Hemorrhage. II. Alterations in heart rate and arterial pressure during 50 percent blood volume loss in the conscious animal-Hannon *et al***

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*James W. Marqusee 16 July 81*  
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were made. Thereafter, 50 percent of the estimated blood volume was removed progressively over a one-hour period. No physiological changes were seen until blood loss exceeded 10 percent. A transient increase in heart rate occurred at 20 percent loss, but subsequent rates were no different from control values. Systolic, diastolic, and mean arterial pressures decreased progressively between 20 and 50 percent blood loss; the respective values at 50 percent blood loss were  $84 \pm 3.2$ ,  $31 \pm 3.2$ , and  $49 \pm 2.8$  mm Hg. Because of the functional similarities of the human and porcine cardiovascular systems, studies of severe hemorrhage in the recumbent conscious pig may provide reliable physiological information which will be useful in recognizing the consequences of massive hemorrhage in humans, such as from injuries incurred during combat.

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## ABSTRACT

A porcine animal model, designed to simulate physiologic characteristics of the combat casualty, was used to assess the effects of severe blood loss on the heart rate and arterial pressures in the absence of anesthesia or other interventions. Chronic catheters were placed surgically in the aorta, via the carotid artery, of 8 young domestic pigs. Seven to 9 days after surgery each animal was brought into the laboratory and the catheter was connected to a three-way stopcock and a pressure transducer for blood removal and pressure recording. After 30 minutes of unrestrained and uninterrupted supine rest, control measurements were made. Thereafter, 50 percent of the estimated blood volume was removed progressively over a one-hour period. No physiological changes were seen until blood loss exceeded 10 percent. A transient increase in heart rate occurred at 20 percent loss, but subsequent rates were no different from control values. Systolic, diastolic, and mean arterial pressures decreased progressively between 20 and 50 percent blood loss; the respective values at 50 percent blood loss were  $84 \pm 3.2$ ,  $31 \pm 3.2$ , and  $49 \pm 2.8$  mm Hg. Because of the functional similarities of the human and porcine cardiovascular systems, studies of severe hemorrhage in the recumbent conscious pig may provide reliable physiological information which will be useful in recognizing the consequences of massive hemorrhage in humans, such as from injuries incurred during combat.

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## PREFACE

This is the second in a series of reports on the physiological responses of domestic swine to severe hemorrhage. The first report dealt with procedures for chronic implantation of arterial and venous catheters to allow hemodynamic and biochemical studies in the conscious animal. Future reports will be concerned with the blood gas and acid-base status, blood biochemical characteristics, blood volume changes, and tissue blood flow alterations in conscious pigs recovering spontaneously from hemorrhagic hypotension.

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The mongrel dog has been used almost exclusively in animal studies of severe blood loss and hemorrhagic shock. In large measure this is attributable to the ready availability, tractability, and traditional use of the dog as an animal model for human-oriented biomedical research. Such traditional use, however, does not necessarily signify close similarities in human and canine physiology. In fact, many marked functional differences exist, and certain of these could play an influential role in the outcome of compensatory responses to severe blood loss. The dog, for example, has a far higher cardiovascular reserve (1,2) and aerobic capacity (3,4) than man; hence, one would expect the dog to have a greater functional capacity to compensate for severe blood loss. In addition, dogs differ significantly from men in terms of the bicarbonate buffer capacity of arterial blood (5) and the characteristics of tissue blood flow redistribution during high cardiac output states (1,6,7). Any of these functional variables could influence the outcome of severe blood loss studies.

On the basis of limited available evidence, the domestic pig would appear superior to the dog as a large animal model for studies directed at the cardiovascular consequences of severe blood loss. The functional characteristics of the pig cardiovascular system more closely resemble those of man than do the characteristics of the dog (8,9). During severe exercise, for instance, the pig and human, in contrast to the dog and human, show remarkably similar changes in cardiac output and organ blood flow distribution (2). Indeed, the recognition of such similarities has led in recent years to increased but still limited use of pigs for research on cardiovascular function during and following hemorrhage (10-15). Most investigations have involved anesthetized animals, a condition that seriously modifies normal responses to blood loss (15), or have employed the Wiggers model (16) to study the characteristics of irreversible shock. Neither of these experimental conditions has much relevancy to the clinical shock problems seen in humans (10,17). Reports on the cardiovascular consequences of hemorrhage in conscious swine are rarely seen, and those that are available (14,18,19) are of limited scope. The present investigation, therefore,

was initiated to delineate heart rate and arterial pressure responses to incremental blood loss, up to and including 50 percent of the calculated blood volume.

#### METHODS

Eight young domestic swine, both gilts and barrows, were used in this study. They were obtained from a commercial hog farm (J.G. Boswell Company, P.O. Box 457, Corcoran, CA 93212) and were housed as a group in a large indoor animal facility until ready for the surgical emplacement of arterial catheters. At this time each animal to be studied received an intramuscular preanesthetic injection of 0.08 mg/kg atropine, 2.2 mg/kg ketamine HCl, and 1.1 mg/kg zylazine HCl while confined to a portable transport cage. Anesthesia was subsequently induced with a halothane in oxygen mixture administered by a mask placed over the snout. During surgery, anesthesia was maintained with the same mixture by means of a cuffed endotracheal tube and ventilator (Ohio Medical Products).

As described in detail elsewhere (20), the procedure for the construction and placement of a carotid artery catheter in each pig was modified somewhat from that described by Mills and Simmons (21). Briefly, the intravascular portion was prepared from Silastic(R) tubing (0.040 inches ID, 0.085 inches OD) (Dow Corning Medical Grade 602-201). At the point of exit from the vessel, this portion was joined to (0.050 inches ID, 0.090 inches OD) Tygon(R) tubing, formulation S-54-IL. This arrangement minimized intravascular clotting, yet provided the physical characteristics needed for long-term durability of the chronic implant along with minimal distortion of arterial pressure characteristics. The Tygon portion was tunneled beneath the skin to the back of the neck where it was exteriorized through a punch wound and capped with a 16-gauge Luer stub adapter (Intramedic) fitted with an Argyle plastic/rubber intermittent infusion cap. The cap minimized microbial contamination problems and allowed catheter flushing with heparinized saline (10 units/ml) as needed to maintain patency. Flushing at the end of surgery and at weekly intervals thereafter was adequate. Cleanliness subsequent to surgery was maintained by a Velcro(R) patch placed over the exteriorized portions and sutured to the skin. This patch also allowed ready access to the catheter in the conscious animal subsequent to the surgery.

After a 7 to 9-day surgical recovery period, each pig was brought into a quiet laboratory in a portable carrying cage and was given a variety of surgical linen bedding. After 15 to 30 minutes of rooting and bedding rearrangement, the animal invariably assumed a recumbent position, at which point the infusion cap was removed and the stub adapter was connected to a 12-inch pressure monitoring/injection line (Cobe Laboratories, Inc.). The latter had been fitted previously with a three-way plastic stopcock (Pharmaseal, Inc.) and filled with heparinized saline. The entire system was then cleansed by withdrawing

10 ml of fluid (blood plus heparinized saline) followed by flushing with 10 ml of fresh heparinized saline. The catheter system was connected to a Statham P23Db pressure transducer by means of a 36-inch pressure monitoring/injection line (Pharmaseal, Inc.), also filled with heparinized saline. The transducer, suspended by clamps on a ring stand located just outside the portable cage, was height adjusted to match heart level in the recumbent animal. Transducer output was monitored with a Gould (Brush) 220 physiological recorder.

In pilot studies not reported here, cardiovascular functions in the conscious pig were found to vary erratically unless a metabolic steady state had been established and was maintained before baseline measurements were made. Consequently, control values in this study were obtained only after 30 minutes or more of uninterrupted recumbent rest. At the end of the rest period, three sets of measurements were made at 10-minute intervals and average control values were calculated. Included in these measurements were heart rate, systolic pressure, diastolic pressure, and pulse pressure.

Immediately after the control measurements, the hemorrhage procedure was started. Ultimately, 50 percent of the estimated total blood volume was removed over a one-hour period. Estimates of blood volume were calculated on the basis of the regression equation for swine reported by von Engelhardt (9):

$$TBV/kg = 95 \text{ (body wt in kg)}^{-0.068}$$

The one-hour period of hemorrhage was selected arbitrarily to simulate a period of severe hemorrhage such as might be seen in combat casualties. The rate of blood loss was based, again arbitrarily, on an exponential scale such that 10 percent increments of the total blood volume were removed uniformly over successive intervals of 9, 10, 11.5, 13.5, and 16 minutes. To avoid computational errors in determining total blood volume and the 10 through 50 percent volume increments, a suitable program was developed for the Texas Instruments Programmable 59 Calculator used in conjunction with a PC100A printer (Appendix A). At the end of each 10-percent increment of blood volume reduction the above indicated heart rate and arterial pressure measurements were made. Subsequent to hemorrhage, the pigs were returned to the animal housing facility where they remained for 24 hours to determine survivability. Thereafter, they were euthanized.

The accumulated data from this experiment were evaluated with single factor (repeated measures) analyses of variance. In addition, the mean and standard error of the mean values were calculated, and Newman-Keuls tests were used to evaluate between mean differences. Statistically significant effects were assumed when  $P \leq 0.05$ .

## RESULTS

As judged by 24-hour survival beyond the hemorrhagic episode, all of the pigs adequately compensated for 50 percent loss of their estimated blood volume. This does not mean there were no untoward symptoms. They all appeared to hyperventilate, as evidenced by an increase in respiratory rate, at 20 to 30 percent blood loss and seven of the eight pigs experienced nausea severe enough to produce vomiting when blood loss exceeded 40 percent.

The objective data collected during this study are summarized in Figures 1 through 5 (Appendix B) and Table 1. The body weight, estimated blood volume calculated by von Engelhardt's regression equation (9), and the volume of blood removed during hemorrhage period are listed in Table 1. Figures 1 through 5 present heart rate and arterial pressure values (mean  $\pm$  SEM) for the pre-hemorrhage control condition and for 10, 20, 30, 40, and 50 percent blood loss. An analysis of variance summary applicable to graphic data is contained in Table 2.

Table 1. Estimated total blood volume and hemorrhage blood loss of individual pigs

Pig No.	Body Weight kg	Est Blood Volume ml	ml/kg	Hemorrhage ml	ml/kg
24	21.8	1680	77.0	840	38.5
29	28.2	2133	75.7	1067	37.8
36	22.7	1746	76.9	873	38.5
39	23.2	1778	76.6	889	38.3
41	26.8	2037	76.0	1019	38.0
51	25.5	1940	76.1	970	38.0
53	21.4	1648	77.0	824	38.5
54	20.5	1583	77.2	791	38.2
Mean	23.8	1818	76.6	909	38.3
SEM	$\pm 0.09$	$\pm 69.7$	$\pm 0.20$	$\pm 34.9$	$\pm 0.11$

Table 2. Analysis of variance summary: Heart rate and arterial pressures during hemorrhage

Variable	Mean Square	F
Heart rate	1006.7	6.72*
Mean arterial pressure	5516.8	80.6*
Systolic pressure	3664.5	65.7*
Diastolic pressure	5125.7	67.9*
Pulse pressure	158.3	4.88*

\*Significant at  $P < 0.05$

Heart rate, Figure 1, was transiently elevated from a control value of  $112 \pm 4.0$  beats per minute to a peak value of  $136 \pm 5.4$  beats per minute at the 20 percent stage of blood loss. After 40 and 50 percent blood loss the rates appeared somewhat subnormal relative to the control value but, as evaluated by Newman Keuls test, this apparent effect was not statistically significant. In fact, the significant F value for heart rate seen in Table 2 was entirely attributable to the tachycardia observed after 20 percent blood loss.

Mean, systolic, and diastolic pressures showed a significant overall decline over the course of 50 percent blood loss (Figures 2,3,4). Accordingly, during the hemorrhagic episode, mean arterial pressure decreased from  $114 \pm 3.7$  to  $49 \pm 2.8$  mm Hg, systolic pressure from  $134 \pm 2.4$  to  $84 \pm 3.2$  mm Hg, and diastolic pressure from  $93 \pm 2.8$  to  $31 \pm 3.2$  mm Hg. In all instances, the apparent decrease between control and 10 percent blood loss was not statistically significant. Significant decrements were only observed after more than 10 percent of the estimated blood volume had been removed. Furthermore, the apparent decrements in systolic pressure (Figure 3) were not statistically significant after the blood volume loss reached 30 percent; beyond 30 percent, the decrements in mean and diastolic pressure were significant.

Largely because of the late attenuation of the systolic hypotensive response, pulse pressure (Figure 5) showed a slight but significant increase commencing at 40 percent blood loss. The control value

was  $42 \pm 2.1$  mm Hg while the 50 percent value was  $53 \pm 2.1$  mm Hg.

#### DISCUSSION

Insofar as can be determined, only Simon and Olsen (14) have reported data on hemorrhage in conscious domestic pigs that can be directly compared to the data reported here. These investigators (14) studied 34 immature (8 to 10-weeks old, 8 to 12 kg) animals and measured mean aortic blood pressure after hemorrhages of 10, 20, 30, and 40 percent of the estimated blood volume. Their estimate of total blood volume was slightly less than that based on the von Engelhardt regression equation (9). It was thus assumed to be 7.5 percent of the body weight, whereas the von Engelhardt equation would give a value of 8.1 percent of body weight for pigs averaging 10 kg. In any event, hemorrhage in their study (14) was associated with a progressive decline in mean pressure, from an average control value of about 141 mm Hg to an average value of about 49 mm Hg after 40 percent blood loss. Neither of these values is consistent with those reported here; their control value is considerably higher and their 40 percent hemorrhage value is somewhat lower than the corresponding mean pressures observed in the present investigation. It is, perhaps, important in this regard that Simon and Olsen (14) made their measurements 24 to 48 hours after surgical implantation of arterial catheters, whereas 7 to 9 days intervened in the present study. In addition, Simon and Olsen (14) do not mention any effort to obtain a steady metabolic state prior to the recording of control values, nor do they indicate whether their animals were in a recumbent, standing, or in some sort of physically restrained condition at the time the mean pressure measurements were made. Finally, they do not state the time interval over which blood was removed or how their values of mean pressure were obtained, i.e., an arithmetic average of systolic and diastolic pressure or an electronically integrated mean pressure as used in the present investigation. Any of the foregoing variables could account for the differences obtained in the two studies.

In a companion paper, Simon and Olsen (15) compared mean arterial pressures of conscious and anesthetized (pentobarbital, 27.5 mg/kg) pigs. They found the latter were more markedly affected by hemorrhage than the former. In the anesthetized group mean pressure after 20 percent blood loss was nearly the same, about 50 mm Hg, as after 40 percent loss in the conscious group. At 40 percent loss, the anesthetized animals had a mean arterial pressure of about 20 mm Hg. Elsewhere, similar effects of anesthesia are seen. Hobler and Napodano (10), for instance, reported marked decrements in the mean arterial pressure of 20 to 40 kg pigs subjected to 40 percent hemorrhage (based on blood volume equaling 6.5 percent of body weight). In fact, only one of seven animals so studied survived a two-hour post-hemorrhage observation period. This contrasts to 24-hour survival of all animals in the present study. As noted by Simon and Olsen (15), a variety of factors could account for the deleterious effect of anesthesia in the

hemorrhaged animal. Pentobarbital reduces venomotor tone (22) and disrupts the venous compensatory response to hypovolemia (23). Anesthesia also decreases cardiac output (24,25), vasomotion (26-29), and total peripheral resistance (27), and as a result, the regional distribution of blood flow is altered (15,27,29).

How closely do the functional alterations associated with hypovolemia in swine approximate those observed in humans? This question cannot be answered with certainty at the present time, largely because so few controlled experimental studies have been done in either pigs or humans. The preponderance of observations on humans have been made under clinical conditions, in most instances subsequent to an accidental hemorrhagic episode. Thus, only crude estimates of blood loss were possible and compensatory responses, undoubtedly, had progressed to varying degrees. In spite of these limitations, available evidence seems to suggest that tolerance to blood loss, in terms of survival at least, is roughly the same in pigs and men. Accordingly, in studies conducted in World War II (30) wounded soldiers ( $N = 16$ ) subjectively classified by medical personnel as being in a state of severe hypovolemic shock, yet survived, had systolic pressure ranging from 0 to 80 mm Hg ( $49 \pm 7.6$  mm Hg average), diastolic pressure ranging from 0 to 68 mm Hg ( $25 \pm 5.8$  mm Hg average), and pulse pressure ranging from 0 to 58 mm Hg ( $24 \pm 4.7$  mm Hg average). Heart rates averaged  $116 \pm 3.3$  beats per minute. Estimates of blood loss averaged  $33 \pm 4.2$  percent on the basis of Evans Blue dilution measurements corrected for resuscitation fluids that were administered. On the basis of hemoglobin measurements, also corrected for resuscitation fluid administration, estimated blood loss averaged  $54 \pm 4.3$  percent. Except for tachycardia and reduced pulse pressure, these human values were not too different from those seen in the present study. The exceptions could be due to a variety of factors, including the time lapse between hemorrhage, the experimental measurements, and treatment with resuscitation fluids, surgery, and so forth.

More akin to the present investigation, Stone et al (31) induced "acute hemorrhagic shock," as they termed it, in 10 conscious human volunteers by removing 24 to 56 percent (average, 40 percent) of the estimated total blood volume. Immediately after hemorrhage mean arterial blood pressure in these subjects averaged 48 mm Hg, a value that approximated the 49 mm Hg seen after 50 percent, but considerably lower than the 63 mm Hg seen after 40 percent hemorrhage in the present study of swine. On the basis of these comparisons, therefore, pigs appear to be somewhat more tolerant of blood loss than humans. Stone et al (31) reported no values for heart rate, systolic, diastolic, or pulse pressure. However, Shenkin et al (32) showed that as long as the supine position was maintained in human subjects, as much as 1000 ml of blood might be lost before significant increase in pulse rate was observed. If 1000 ml is assumed to represent 20 percent of the blood volume in humans, this observation seems consistent with the response observed here with pigs.

Direct comparison of the present data to those reported for canine hemorrhage is not yet possible because, insofar as can be determined, equivalent experiments have not yet been performed. Most canine studies involved rapid loss of blood, typically on the order of minutes, and in recent years such studies have been conducted largely in anesthetized preparations. Nevertheless, certain of the responses recorded in dogs would seem pertinent not only to the results reported here but also to the question of relevancy of canine and porcine animal models to results in humans.

In at least one respect, the arterial pressure changes associated with progressive hemorrhage are similar in dogs and pigs. Both species show little change in mean pressure during the early stages of blood loss, and relatively large amounts of blood may be removed before marked decrements in pressure are observed. This characteristic was first described in rabbits by Porter (33) who postulated the existence of a critical level of blood pressure during hemorrhage. According to Porter (33), if the arterial pressure was at the critical level, additional blood loss would begin to impinge on arterial volume, in contrast to earlier impingement on venous volume, and would thus cause a precipitous decline in arterial pressure. In dogs, data consistent with this concept have been reported by Blalock (34) and Swingle et al (35). Comparable data for swine are found in Figures 2 and 3.

Progressive hemorrhage over a one-hour period allows sufficient time for the manifestation of compensatory responses which ameliorate the potentially deleterious actions of blood loss. Prominent among these compensations is hemodilution and consequent increases in plasma volume, presumably attributable to the Starling effect (36). In the present study, such hemodilution limited the actual blood volume reduction to about 40 percent, even though 50 percent of the initial blood volume was removed (unpublished data). Similar hemodilution, particularly during the first few hours after rapid blood loss, has been a consistent finding in dogs (34,35,37-39) and humans (40,41). Studies with dogs, furthermore, have shown that hemodilution can markedly influence the amount of blood that can be lost before hypotension and shock ensue; the longer the hemorrhage interval, the greater the amount of blood that can be removed without fatal consequences (34,35). An extreme example of this is found in a study reported by Elman et al (42) in which it was shown that nearly twice the initial blood volume could be removed without fatal consequences if the amount of blood removed at each hemorrhage was small (10 ml/kg) and the bleeding periods were spaced 24 hours apart.

The large erythrocyte storage capacity of the canine spleen appears to afford a second compensatory mechanism that has little or no impact in swine and humans. As long ago as 1920, Hooper et al (43) reported that when the hematocrit was lowered by hemorrhage, total circulating erythrocyte volume exceeded the value predicted on the

basis of the volume of erythrocytes removed. Later, Lehman and Amole (44) found that resistance to hemorrhage in terms of blood pressure decrement and survival was markedly less in splenectomized as compared to intact dogs, and Lewis et al (45) showed with an exteriorized spleen preparation that hemorrhagic hypotension caused a 50 percent reduction in the splenic size. The latter investigators (45) concluded that the red cells delivered to the blood by splenic contraction led to an improvement in venous return, hence survival. Finally, Walcott (46) showed in surviving dogs that 17 percent of lost erythrocytes were replaced, as compared to 11 percent of lost plasma, during the first hour after rapid but severe blood loss. In fact, in these experiments, Walcott (46) found that erythrocyte mobilization resulted in an elevated hematocrit immediately after hemorrhage, a response opposite to that seen in pigs and humans. In terms of the splenic contribution to the compensation for hemorrhagic hypotension, therefore, the pig, because of a much smaller spleen size, would seem more like the human than the dog. It should be noted, however, that this supposition has yet to be verified by experimental data.

#### CONCLUSIONS

- The heart rate and arterial pressure changes associated with severe hemorrhage in conscious swine are remarkably similar to those reported for conscious humans. The pig may tolerate a somewhat greater blood loss than man without fatal consequences, but this has yet to be established.
- On the basis of results reported in the literature, anesthetic agents seriously modify the physiological responses to hemorrhage. Equivalent blood loss causes a far greater decrease in arterial pressure in the anesthetized animal as compared to the conscious animal. The conscious pig survives much greater blood losses than the anesthetized pig.
- The pig would appear to be superior to the dog for human oriented studies of physiological compensations to severe blood loss. The large erythrocyte storage capacity of the canine spleen plays a major compensatory role in the restoration of blood volume following hemorrhage -- a role that is not nearly so important in the human and pig.

#### RECOMMENDATIONS

- Detailed studies of the compensatory responses to massive non-fatal hemorrhage should be conducted in the conscious pig. Such studies should include measurements of hemodynamic changes, acid-base status, oxygen transport capacity, blood metabolite changes, and tissue fluid transfer to the vasculature.

- The key physiologic changes leading to fatality following massive hemorrhage need to be delineated in the conscious pig.

## REFERENCES

1. ROWELL, L.B. Human cardiovascular adjustments to exercise and thermal stress. *Physiol Rev* 54:75-259, 1974
2. SANDERS, M., S. RASMUSSEN, D. COOPER, and C. BLOOR. Renal and intrarenal blood flow distribution in swine during swine exercises. *J Appl Physiol* 40:932-935, 1976
3. DILL, D.B. Comparative physiology of oxygen transport. *J Sports Med Phys Fitness* 3:191-200, 1963
4. ROWELL, L.B. Circulation to skeletal muscle. In: *Physiology and Biophysics: Circulation, Respiration and Fluid Balance*, edited by T.C. Ruch, H.D. Patton, and A.M. Scher. Philadelphia, PA: W.B. Saunders Co., 1974. pp 200-214
5. RODKEY, W.G., J.P. HANNON, J.G. DRAMISE, R.D. WHITE, D.C. WELSH, and B.N. PERSKY. Arterialized capillary blood used to determine the acid-base and blood gas status of dogs. *Am J Vet Med Res* 39:459-464, 1978
6. DELGADO, R., T.M. SANDERS, and C.M. BLOOR. Renal blood flow distribution during steady state exercise and exhaustion in conscious dogs. *J Appl Physiol* 39:475-478, 1975
7. VATNER, S.F., C.B. HIGGINS, S. WHITE, T. PATRICK, and D. FRANKLIN. The peripheral vascular response to severe exercise in untethered dogs before and after complete heart block. *J Clin Invest* 50: 1950-1960, 1971
8. DOUGLAS, W.R. Of pigs and men and research: A review of applications and analogies of the pig, *Sus scrofa*, in human medical research. *Space Life Sci* 3:226-234, 1972
9. von ENGLEHARDT, W. Swine cardiovascular research -- a review. In: *Swine in Biomedical Research*, edited by L.K. Bustad and R.O. McClellan. Seattle, WA: Frayn Printing, 1966. pp 307-329
10. HOBLER, K.E., and R.J. NAPODANO. Tolerance of swine to acute blood volume deficits. *J Trauma* 14:716-718, 1974
11. LEVINE, B.A., W.H. SCHWESINGER, K.R. JONES, and B.A. PRUITT, JR. Cimetidine prevents reduction in gastric mucosal blood flow during shock. *Surgery* 84:113-119, 1978
12. LINDBERG, B. Liver and metabolism in hemorrhagic shock. An experimental study with special reference to the effect of glucagon. *Acta Chir Scand*, Suppl 476, 1977

13. BECKER, H.C., R.M. SEUFERT, and L. GERSTENBERGK. Erfahrungen mit dem haemorrhagischen Schock beim Ferkel. *Res Exp Med (Berlin)* 170:125-131, 1977
14. SIMON, M.A., and W.R. OLSEN. Capillary flow in hemorrhagic shock. I. Hemorrhage in the nonanesthetized pig. *Arch Surg* 99:631-633, 1969
15. SIMON, M.A., and W.R. OLSEN. Capillary flow in the anesthetized pig. II. Hemorrhage in the anesthetized pig. *Arch Surg* 99:634-636, 1969
16. WERLE, J.M., R.S. COSBY, and C.J. WIGGERS. Observations on hemorrhagic hypotension and hemorrhagic shock. *Am J Physiol* 136:401-420, 1942
17. MOORE, F.D. Relevance of experimental shock studies to clinical shock problems. *Fed Proc* 9:227-232, 1961
18. STREMPLE, J.E., H. THOMAS, V. SAKACH, and D. TRELKA. Myocardial utilization of hypertonic glucose during hemorrhagic shock. *Surgery* 80:4-13, 1974
19. CAREY, L.C., R. CURTIN, and J.D. SAPIRA. Influence of hemorrhage on adrenal secretion, blood glucose and serum insulin in the awake pig. *Ann Surg* 183:185-192, 1976
20. DIXON, R.S., P.B. JENNINGS, JR., and J.P. HANNON. Physiologic aspects of porcine hemorrhage. I. A vascular catheter for chronic implantation in swine. Report No. 93. San Francisco, CA: Letterman Army Institute of Research, 1981
21. MILLS, L.J., and D.H. SIMMONS. An arterial catheter for chronic implantation in dogs. *J Appl Physiol* 23:285-286, 1967
22. ECKSTEIN, J.W., W.K. HAMILTON, and J.J. McCAMMOND. The effect of thiopental on peripheral venous tone. *Anesthesiology* 22:525-528, 1961
23. DOW, R.W., and W.J. FRY. Venous compensatory mechanisms in acute hypovolemia. *Surg Gynecol Obstet* 125:511-515, 1967
24. HEILBRUNN, A., and F.F. ALLBRITTON. Cardiac output during and following surgical operations. *Ann Surg* 152:197-210, 1960
25. NASH, C.B., F. DAVIS, and R.A. WOODBURY. Cardiovascular effects of anesthetic doses of pentobarbital sodium. *Am J Physiol* 185:107-112, 1956

26. CHAMBERS, R., and B.W. ZWEIFACH. Topography and function of the mesenteric capillary circulation. *Am J Anat* 75:173-205, 1944
27. GREISHEIMER, E.M. The circulatory effects of anesthesia. In: *Handbook of Physiology. Circulation.* Vol 3, Sect 2. Washington, DC: American Physiological Society, 1965. pp 2477-2510
28. WEBB, R.C., and P.A. NICOLL. The batwing as a subject for studies in homeostasis of capillary bids. *Anat Rec* 120:253-263, 1964
29. ZWEIFACH, B.W. Direct observation of mesenteric circulation in experimental animals. *Anat Rec* 120:277-291, 1954
30. DEPARTMENT OF THE ARMY. Office of the Surgeon General. The Board for the Study of the Severely Wounded. *Surgery in World War II. Physiologic Effects of Wounds*, edited by H.K. Beecher. Washington, DC, 1952
31. STONE, H.H., C.D. DONNELLY, T.N. MACKRELL, B.J. BRANDSTATER, and P. NEMIR, JR. The effect of acute hemorrhagic shock on cerebral circulation and metabolism in man. In: *Shock and Hypotension: Pathogenesis and Treatment. The Twelfth Hahnemann Symposium*, edited by L.C. Mills and H.H. Mayer. New York: Grune and Stratton, 1965. pp 257-264
32. SHENKIN, H.A., R.H. CHENEY, S.R. GOVONS, J.D. HARDY, and A.G. FLETCHER, JR. On the diagnosis of hemorrhage in man. A study of volunteers bled large amounts. *Am J Med Sci* 208:421-436, 1944
33. PORTER, W.T. Shock from fat embolism of the vasomotor center. *Am J Physiol* 71:277-315, 1924/1925
34. BLALOCK, A. Mechanism and treatment of experimental shock; shock following hemorrhage. *Arch Surg* 15:762-798, 1927
35. SWINGLE, W.W., J.J. PFIFFNER, H.M. VARS, and S.M. PARKINS. The effect of hemorrhage on the normal and adrenalectomized dog. *Am J Physiol* 107:259-274, 1934
36. STARLINE, E.H. On the absorption of fluids from the connective tissue spaces. *J Physiol (London)* 19:312-326, 1896
37. CALVIN, D.B. Plasma volume and plasma protein concentration after severe hemorrhage. *J Lab Clin Med* 26:1144-1148, 1940/1941
38. ELMAN, R., C.E. LISCHER, and H.W. DAVEY. Plasma proteins (albumin and globulin) and red cell volume following a single severe hemorrhage. *Am J Physiol* 138:569-576, 1942

39. EBERT, R.V., E.A. STEAD, JR., J.V. WARREN, and W.E. WATTS. Plasma protein replacement after hemorrhage in dogs with and without shock. *Am J Physiol* 136:299-305, 1942
40. ELMAN, R. Acute protein deficiency (hypoproteinemia) in surgical shock due to severe hemorrhage and burns, intestinal obstruction and general peritonitis, with surgical reference to use of plasma and hydrolized protein. *J Am Med Assoc* 120:1176-1180, 1942
41. EBERT, R.V., E.A. STEAD, JR., and J.G. GIBSON. Response of normal subjects to acute blood loss with special reference to the mechanism of restoration of blood volume. *Arch Intern Med* 68:578-590, 1941
42. ELMAN, R., C. LISCHER, and H.W. DAVEY. Red cell volume, plasma albumin and globulin in fatal surgical shock due to repeated hemorrhage. *Am J Physiol* 140:737-741, 1943
43. HOOPER, C.W., H.P. SMITH, E.A. BELT, and G.H. WHIPPLE. Blood volume studies. I. Experimental control of a dye blood volume method. *Am J Physiol* 51:205-220, 1920
44. LEHMAN, E.P., and C.V. AMOLE. Function of the spleen in retardation of shock from hemorrhage; experimental study. *Surgery* 4:44-50, 1938
45. LEWIS, R.M., J.M. WERLE, and C.J. WIGGERS. The behavior of the spleen in hemorrhagic hypotension and shock. *Am J Physiol* 138: 205-211, 1943
46. WALCOTT, W.W. Blood volume in experimental hemorrhagic shock. *Am J Physiol* 143:247-253, 1945

Program utilizing Texas Instruments T159 calculator with PC100 printer to record animal number and body weight in pounds, and to complete body weight in kilograms, blood volume in milliliters, and blood loss as percentage of blood volume.

APPENDIX A

## I. Printer readout and user instructions

<u>Printer Readout</u>	<u>Operational Step</u>
	1. Program calculator manually or with magnetic card.
SWINE BLOOD VOLUME	2. Initiate program: press user defined key A.
54. ND	3. Enter pig No.: Press R/S.
45. LB	4. Enter body wt: press R/S.
20. 45454545	Body weight in kg computed.
1582. 631823	Blood volume in ml computed.
	5. Subroutine to compute ml blood loss corresponding to predetermined percent of blood volume: press user defined key B.
10. 158. 2601823	6. Enter desired %: press R/S volume computed.
35. 553. 9209982	Repeat step 6
22. 348. 1788692	Repeat step 6.
	7. Subroutine to compute percentage of total blood volume lost when amount removed is known: press user defined key C.

APPENDIX (Cont)

<u>Printer Readout</u>		<u>Operational Step</u>
63. 3.980712567	ML %	8. Enter amount: press R/S percent computed.
169. 10.67811943	ML %	Repeat step 8.
387. 24.45294963	ML %	Repeat step 8.
		9. Subroutine to advance printer paper 4 spaces: press user defined key D.

II. Program Listing:

<u>Step, Code, Key</u>	<u>Function</u>
000 76 LBL	
001 11 A	
002 69 OP	
003 00 00	
004 03 3	
005 06 6	
006 04 4	
007 03 3	
008 02 2	
009 04 4	
010 03 3	
011 01 1	
012 69 OP	Initiate program and print title:
013 01 01	"Swine Blood Volume"
014 01 1	
015 07 7	
016 00 0	
017 00 0	
018 01 1	
019 04 4	
020 02 2	
021 07 7	
022 03 3	
023 02 2	
024 69 OP	

APPENDIX (Cont)

<u>Step</u>	<u>Code</u>	<u>Key</u>	<u>Function</u>
025	02	02	
026	03	3	
027	03	3	
028	04	4	
029	06		
030	00		
031	00		
032	04	4	
033	02	02	
034	02	02	
035	02	02	
036	69	DP	
037	03	03	
038	00		
039	03	03	
040	04		
041	01	1	
042	03	03	
043	00		
044	01	1	
045	07		
046	00	0	
047	00	0	
048	69	DP	
049	04	04	
050	69	DP	
051	05	05	
052	98	RDV	
053	98	RDV	
054	03	3	
055	01	1	
056	03	3	
057	02	2	
058	69	DP	Enter pig number and print label: "No"
059	04	04	
060	91	RNS	
061	69	DP	
062	06	06	
063	98	RDV	
064	02	2	
065	07	7	Enter pig weight in pounds, store and print label: "LB"
066	01	1	
067	04	4	
068	69	DP	
069	04	04	

APPENDIX (Cont)

<u>Step, Code, Key</u>	<u>Function</u>
070 91 RCL	
071 82 STO	
072 01 01	
073 69 DP	
074 06 06	
075 02 0.6	
076 06	
077 02	
078 02 0.2	
079 69 DP	
080 04 04	
081 43 RCL	
082 01 01	
083 55 +	Compute body weight in
084 02 2	kilograms, store, and
085 93 =	print with label: "KG"
086 02 =	
087 95 =	
088 42 STO	
089 01 01	
090 98 ADV	
091 69 DP	
092 06 06	
093 03 3	
094 00 0	
095 02 2	
096 07 7	
097 69 DP	
098 04 04	
099 09 9	
100 05 5	Compute blood volume from
101 65 X	Engelhardt equation (9),
102 43 RCL	store, and print label:
103 01 01	"ML"
104 45 YX	
105 93 =	
106 00 0	
107 06 0.6	
108 08 0.8	
109 94 =	
110 95 =	
111 65 X	
112 43 RCL	
113 01 01	

APPENDIX (Cont)

<u>Step, Code, Key</u>	<u>Function</u>
114 98 ADV	
115 95 =	
116 42 STO	
117 02 02	
118 69 DP	
119 06 06	
120 98 ADV	
121 98 ADV	
122 91 R/S	
123 76 LBL	
124 12 B	
125 06 6	
126 01 1	
127 69 DP	
128 04 04	
129 91 R/S	Enter desired percentage
130 42 STO	of blood loss, store, and
131 03 03	print label "%"
132 69 DP	
133 06 06	
134 03 3	
135 00 0	
136 02 2	
137 07 7	
138 69 DP	
139 04 04	
140 43 RCL	
141 03 03	Compute volume of blood to
142 65 X	be removed and print label:
143 93 .	"ML"
144 00 0	
145 01 1	
146 65 X	
147 43 RCL	
148 02 02	
149 95 =	
150 69 DP	
151 06 06	
152 98 ADV	
153 61 GTO	Recycle to start of subroutine
154 12 B	
155 91 R/S	
156 76 LBL	

APPENDIX (Cont)

<u>Step</u>	<u>Code</u>	<u>Key</u>	<u>Function</u>
157	13	C	
158	98	ADV	
159	03	S	
160	00	0	
161	02	2	
162	07	7	
163	69	DP	Enter measured blood loss
164	04	04	in ml, store, and print
165	91	R/S	label: "ML"
166	43	GTO	
167	03	03	
168	69	DP	
169	06	06	
170	06	6	
171	01	1	
172	69	DP	
173	04	04	
174	43	ROL	
175	03	03	
176	55	+	
177	43	ROL	Compute percent and print
178	02	02	with label: "%"
179	65	X	
180	01	1	
181	00	0	
182	00	0	
183	95	=	
184	69	DP	
185	06	06	
186	61	GTO	
187	13	C	Recycle to start of subroutine
188	98	ADV	
189	91	R/S	
190	76	LBL	
191	14	D	
192	98	ADV	Subroutine to advance printer
193	98	ADV	4 spaces
194	98	ADV	
195	98	ADV	
196	91	R/S	

**Figure 1**

Pulse rate of conscious swine during hemorrhage to 50 percent of the estimated blood volume. Ordinate values in beats per minute.

**Figure 2**

Mean arterial pressure of conscious swine during hemorrhage to 50 percent of the estimated blood volume. Ordinate values in mm Hg.

**Figure 3**

Systolic pressure of conscious swine during hemorrhage to 50 percent of the estimated blood volume. Ordinate values in mm Hg.

**Figure 4**

Diastolic pressure of conscious swine during hemorrhage to 50 percent of the estimated blood volume. Ordinate values in mm Hg.

**Figure 5**

Pulse pressure of conscious swine during hemorrhage to 50 percent of the estimated blood volume. Ordinate values in mm Hg.

**APPENDIX B**

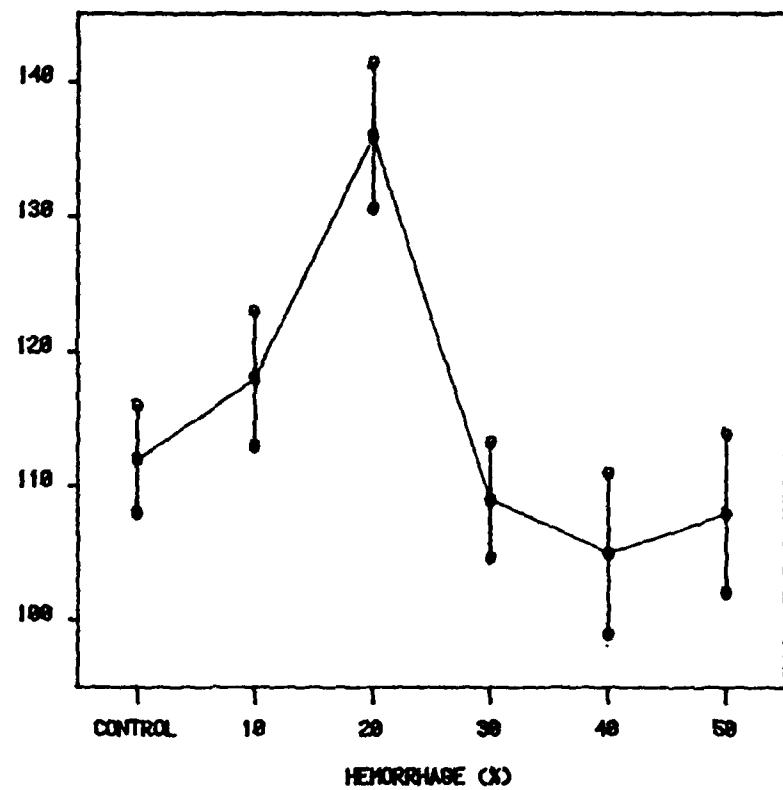


Figure 1. Pulse rate of conscious swine during hemorrhage to 50 percent of the estimated blood volume.  
Ordinate values in beats per minute.

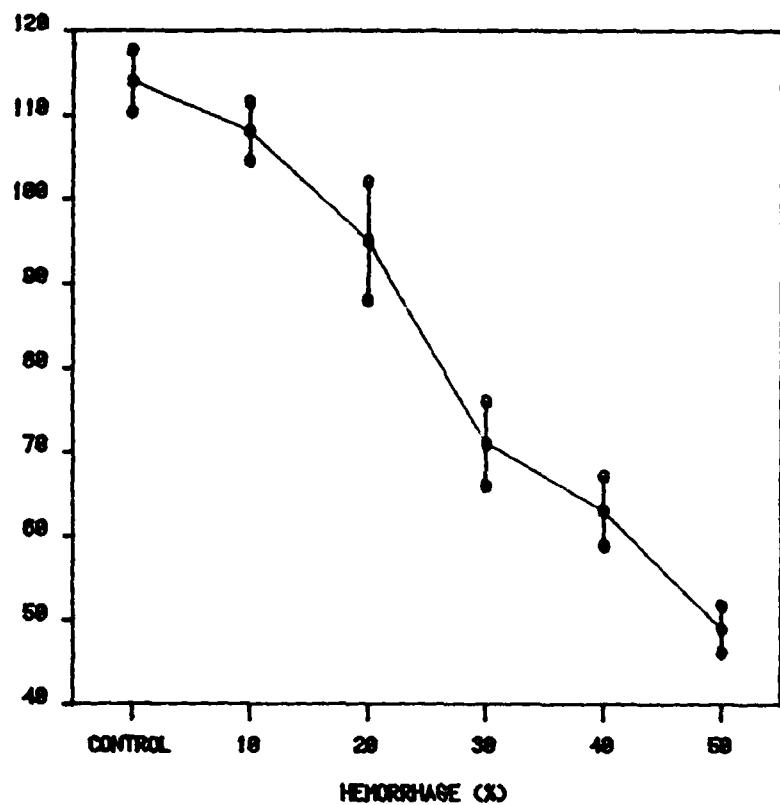


Figure 2. Mean arterial pressure of conscious swine during hemorrhage to 50 percent of the estimated blood volume. Ordinate values in mm Hg.

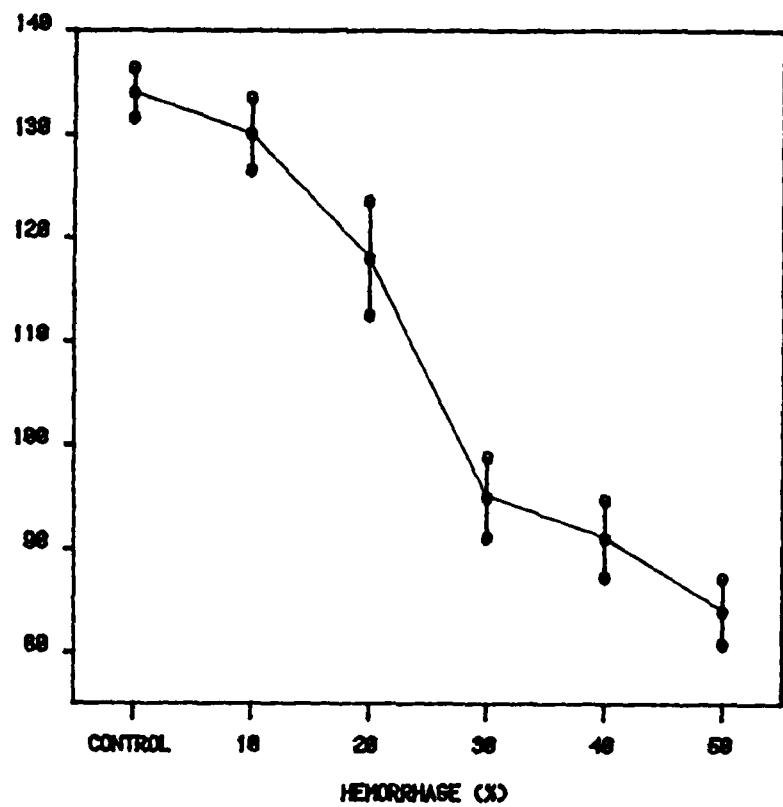


Figure 3. Systolic pressure of conscious swine during hemorrhage to 50 percent of the estimated blood volume. Ordinate values in mm Hg.

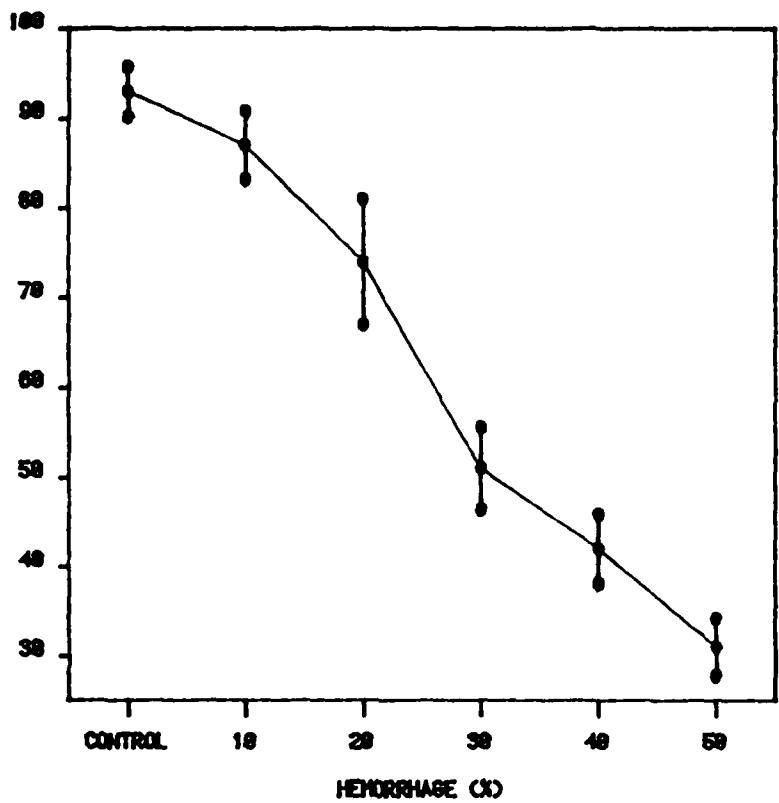


Figure 4. Diastolic pressure of conscious swine during hemorrhage to 50 percent of the estimated blood volume. Ordinate values in mm Hg.

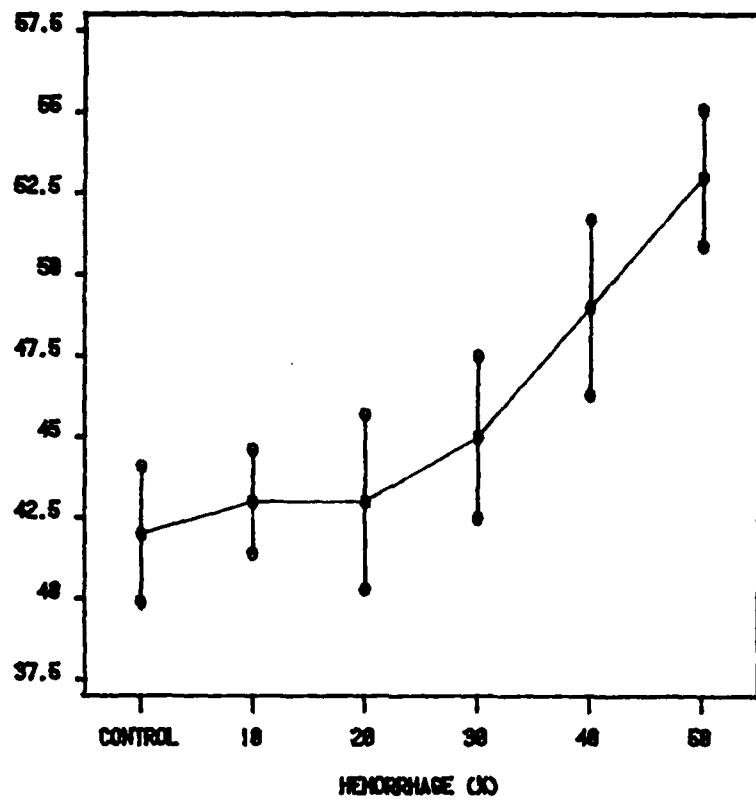


Figure 5. Pulse pressure of conscious swine during hemorrhage to 50 percent of the estimated blood volume. Ordinate values in mm Hg.

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25. LAMSON, P.D., and W.E. De TURK. Studies on shock induced by hemorrhage. XI. A method for the accurate control of blood pressure. *J Pharmacol Exp Therap* 83:250-252, 1945
26. HOBLER, K.E., and R.J. NAPONDANO. Tolerance of swine to acute blood volume deficits. *J Trauma* 14:716-718, 1974
27. SIMON, M.A., and W.R. OLSEN. Capillary flow in hemorrhagic shock. I. Hemorrhage in the nonanesthetized pig. *Arch Surg* 99:631-633, 1969
28. SAPIRSTEIN, L.A. Regional blood flow by fraction distribution of indicators. *Am J Physiol* 193:161-168, 1958
29. SIMON, M.A., and W.R. OLSEN. Capillary flow in hemorrhagic shock. II. Hemorrhage in the anesthetized pig. *Arch Surg* 99:634-636, 1958
30. OLSEN, W.R. Capillary flow in hemorrhagic shock. III. Metaraminol and capillary flow in the nonanesthetized and anesthetized pig. *Arch Surg* 99:637-640, 1969
31. STREMPLE, J.F., H. THOMAS, V. SAKACH, and D. TRELKA. Myocardial utilization of hypertonic glucose during hemorrhagic shock. *Surgery* 80:4-12, 1976
32. STARLING, E.H. On the absorption of fluids from the connective tissue spaces. *J Physiol (London)* 18:312-326, 1896
33. MELLANDER, S. Comparative studies on the adrenergic neurohormonal control of resistance and capacitance blood vessels in the cat. *Acta Physiol Scand* 50 (Suppl 176):1-84, 1975
34. JÄRHÄLT, J. Osmolar control of the circulation in hemorrhagic hypotension. *Acta Physiol Scand* 94 (Suppl. 423):1-84, 1975
35. HADDY, F.J., J.B. SCOTT, and J.I. MOLNAR. Mechanism of volume replacement and vascular constriction following hemorrhage. *Am J Physiol* 208:169-181, 1965
36. ÖBERG, B. Effects of cardiovascular reflexes on net capillary fluid transfer. *Acta Physiol Scand* 71:233-247, 1970
37. ELMAN, R., C. LISHER, and H.W. DAVEY. Red cell volume, plasma albumin and globulin level in fatal surgical shock due to repeated hemorrhage. *Am J Physiol* 140:737-741, 1943
38. SWINGLE, W.W., J.J. PFIFFNER, H.M. VARS, and W.M. PARKINS. The effect of hemorrhage on normal and adrenalectomized dog. *Am J Physiol* 107:259-274, 1934

